

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
7 March 2002 (07.03.2002)

PCT

(10) International Publication Number
WO 02/018404 A3(51) International Patent Classification⁷: C07H 19/06,
19/16, A61K 31/7064, 31/7076, A61P 31/14

(21) International Application Number: PCT/EP01/09633

(22) International Filing Date: 21 August 2001 (21.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0021285.2 30 August 2000 (30.08.2000) GB
0026611.4 31 October 2000 (31.10.2000) GB(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH];
124, Grenzacherstrasse, CH-4070 Basle (CH).(72) Inventors: DEVOS, Rene; 4 Salmon Close, Welwyn
Garden City, Hertfordshire AL7 1TR (GB). DYMOCK,

Brian, William; 15 Vesta Avenue, St. Albans, Hertfordshire AL1 2PJ (GB). HOBBS, Christopher, John; 9 Magnolia Close, Hertford, Hertfordshire SG13 7UR (GB). JIANG, Wen-Rong; 20 Salmon Close, Welwyn Garden City, Hertfordshire AL7 1TR (GB). MARTIN, Joseph, Armstrong; 10 The Chownes, West Common, Harpenden, Herts AL5 2BN (GB). MERRETT, John, Herbert; 23 Bush Spring, Baldock, Hertfordshire SG7 6QT (GB). NAJERA, Isabel; 49 Salisbury Avenue, St. Albans, Hertfordshire AL1 4TZ (GB). SHIMMA, Nobuo; Higashikaigan-Minami 2-11-19, Chigasaki-shi, Kanagawa-ken 253-0054 (JP). TSUKUDA, Takuo; 540-22 Rensyoji, Odawara-shi, Kanagawa-ken 250-0865 (JP).

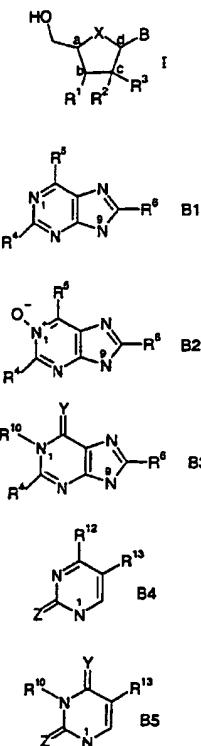
(74) Agent: RAUBER, Beat; 124 Grenzacherstrasse, CH-4070 Basle (CH).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

[Continued on next page]

(54) Title: NUCLEOSIDE DERIVATIVES FOR THE TREATMENT OF HEPATITIS C

Use of compounds of formula I



WO 02/018404 A3



CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

(88) Date of publication of the international search report:
14 November 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/09633A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/06 C07H19/16 A61K31/7064 A61K31/7076 A61P31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 01443 A (WELLCOME FOUND ;KOSZALKA GEORGE WALTER (US); DRAANEN NANINE AGNETA) 20 January 1994 (1994-01-20) examples claims page 3, paragraph 3	1,2,5,6, 8
X	WO 98 16184 A (ICN PHARMACEUTICALS ;AVERTT DEVERON (US); TAM ROBERT (US); WANG GU) 23 April 1998 (1998-04-23) examples claims page 11, line 14	1,15,16

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

5 July 2002

26.07.2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentiaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

de Nooy, A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 01/09633

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 55 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. Claims Nos.: 43, 49-57 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 43,49-57 (all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for claim 43. So many documents were retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the claims. Consequently, the search and the report for this claim has been restricted to the case where R13' ' ' ' is an alkyl but not methyl.

Present claims 49-57 relate to an extremely large number of compounds. In fact, the claims contain so many options, that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the above mentioned claims have been searched insofar as the compounds of claim 49 fall within earlier compound claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (in part), 3-4 (in part), 12-13 (in part), 14, 34, 35, 50-56 (in part)

Compounds of Formula I-a of claim 34 where B' = B2-a of claim 34, and uses, compositions and processes pertaining thereto.

2. Claims: 1 (in part), 3-4 (in part), 15-16 (in part), 17, 36, 37, 50-56 (in part)

Compounds of Formula I-b of claim 36 where B'' = B3-a of claim 36, and uses, compositions and processes pertaining thereto.

3. Claims: 1-4 (in part), 18-25 (in part), 26, 27-28 (in part), 29, 38-42, 50-56 (in part)

Compounds of Formula I-c of claim 38 where B''' = B4-a of claim 38, compounds of Formula I-d of claim 40 where B'''' = B4-b of claim 40 or 41, and uses, compositions and processes pertaining thereto.

4. Claims: 1-4 (in part), 30-32 (in part), 33, 43-48, 50-56 (in part)

Compounds of Formula I-e of claim 43 where B''''' = B5-a of claim 43, compounds of Formula I-f of claim 45 where B'''''' = B5-b of claim 45, compounds of Formula I-g of claim 47 where B'''''''' = B5-c of claim 47 and uses, compositions and processes pertaining thereto.

5. Claims: 1-4 (in part), 5-10, 12-13 (in part), 15-16 (in part), 18-25 (in part), 27-28 (in part), 30-32 (in part), 55-56 (in part)

Use of compounds of the above mentioned claims which do not fall within one of the previous subjects for the treatment of Hepatitis C Virus or for the preparation of a medicament for such treatment.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/09633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 05687 A (UNIV BIRMINGHAM ;WELLCOME FOUND (GB); MILLER JOHN ALLEN (GB); YOUN) 17 March 1994 (1994-03-17) examples claims page 4, line 22 - line 36	1,2, 30-32
A	EP 0 468 352 A (NIPPON KAYAKU KK) 29 January 1992 (1992-01-29) examples claims page 14, line 17	1
X	US 5 102 873 A (MONTGOMERY JOHN A ET AL) 7 April 1992 (1992-04-07) example 3	34
X	US 4 755 594 A (BRIDGES ALEXANDER J ET AL) 5 July 1988 (1988-07-05) example 4	34
X	P.J.M. VAN GALEN ET AL.: "A binding site model and structure-activity relationships for the rat A3 adenosine receptor" MOLECULAR PHARMACOLOGY, vol. 45, 1994, pages 1101-1111, XP008000722 compound 30	34
A	US 5 998 387 A (SCAMMELLS PETER J ET AL) 7 December 1999 (1999-12-07) figure 2	34
A	K. MIURA ET AL.: "Chemical conversion of adenosine to guanosine (Nucleosides and nucleotides. XI)" CHEM. PHARM. BULL., vol. 23, 1975, pages 464-466, XP002190612 chart 1	34
X	W.M. HAMMARGREN ET AL.: "Identification of a novel nucleoside, 1,N6-dimethyladenosine, in human cancer urine" ANALYTICA CHIMICA ACTA, vol. 247, 1991, pages 201-209, XP008005307 compound 1	36
X	US 3 891 623 A (VORBRUGGEN HELMUT ET AL) 24 June 1975 (1975-06-24) examples 2,3	38
		-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H. VORBRÜGGEN ET AL.: "Eine neue einfache Synthese von Cytidinen" LIEBIGS ANN. CHEM., 1975, pages 988-1002, XP002204034 compound 19 —	38
X	X.-X. ZHOU ET AL.: "Pyridyl groups for protection of the imide functions of uridine and guanosine. Exploration of their displacement reactions for site-specific modifications of uracil and guanine bases" ACTA CHEMICA SCANDINAVICA B, vol. 40, 1986, pages 806-816, XP002204035 the whole document —	38
X	R.W. MILES ET AL.: "Nucleic acid related compounds. 87. Nucleophilic functionalization of cytidine and 2'-deoxycytidine derivatives via elaboration of the 4-amino group into a readily displaced 1,2,4-triazol-4-yl substituent" J. ORG. CHEM., vol. 60, 1995, pages 7066-7069, XP002204036 compounds 3,4 —	38
X	G.E. KEYSER ET AL.: "Iodomethyl ethers from 1,3-dioxolane and 1,3-oxothiolane: preparation of acyclic nucleoside analogs" TETRAHEDRON LETTERS, 1979, pages 3263-3264, XP002204037 compound 3 —	38
X	US 4 526 988 A (HERTEL LARRY W) 2 July 1985 (1985-07-02) the whole document —	40
X	HERTEL L W: "SYNTHESIS OF 2-DEOXY-2,2-DIFLUORO-D-RIBOSE AND 2-DEOXY-2,2-DIFLUORO-D-RIBOFURANOSYL NUCLEOSIDES" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 53, no. 11, 27 May 1988 (1988-05-27), pages 2406-2409, XP000572745 ISSN: 0022-3263 the whole document —	40
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHOU T S ET AL: "STEREOSPECIFIC SYNTHESIS OF 2-DEOXY-2,2-DIFLUORORIBONOLACTONE AND ITS USE IN THE PREPARATION OF 2'-DEOXY-2'.2'-DIFLUORO-BETA-D-RIBOFURANOSYL PYRIMIDINE NUCLEOSIDES: THE KEY ROLE OF SELECTIVE CRYSTALLIZATION" SYNTHESIS, GEORG THIEME VERLAG. STUTTGART, DE, no. 6, 1 June 1992 (1992-06-01), pages 565-570, XP000572747 ISSN: 0039-7881 compounds 1,16	40
X	KOTRA L P ET AL: "STRUCTURE-ACTIVITY RELATIONSHIPS OF 2'-DEOXY-2',2'-DIFLUORO-L-ERYTHRO-PENTOFURANOSYL NUCLEOSIDES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 40, no. 22, 1997, pages 3635-3644, XP000867642 ISSN: 0022-2623 compounds 43-52	40
X	KOTRA L P ET AL: "Synthesis of 2,3-dideoxy-2,2-difluoro-1-glycero-pentofuranosyl nucleosides" CARBOHYDRATE RESEARCH, ELSEVIER SCIENTIFIC PUBLISHING COMPANY. AMSTERDAM, NL, vol. 306, no. 1-2, January 1998 (1998-01), pages 69-80, XP004204788 ISSN: 0008-6215 scheme 1	40
X	M. SEKINE, T. NAKANISHI: "Facile synthesis of 3'-O-methylthymidine and 3'-deoxythymidine and related deoxygenated thymidine derivative: A new method for selective deoxygenation of secondary hydroxy groups" J. ORG. CHEM., vol. 55, 1990, pages 924-928, XP002204038 compound 2	43
X	A. HAMPTON ET AL.: "Species- or Isozyme-specific enzyme inhibitors. 5. Differential effects of thymidine substituents on affinity for rat thymidine kinase isozymes" J. MED. CHEM., vol. 25, 1982, pages 644-649, XP002204039 compounds 7d,e	43
		-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. EL-KOUSY ET AL.: "Synthesis and investigation of antiviral activity of 3'-O-(aminoalkyl)-thymidines and their quaternary ammonium salts" MONATSHEFTE FÜR CHEMIE, vol. 125, 1994, pages 713-721, XP002204040 compounds 4a-d, 6a-d ----	43
X	N.K. KOCHETKOV ET AL.: "The mechanism of the reaction of hydroxylamine and O-methylhydroxylamine with cytidine" TETRAHEDRON LETTERS, 1967, pages 3253-3257, XP002204041 compound 4a ----	47, 48
E	WO 01 90121 A (NOVIRIO PHARMACEUTICALS LTD ;UNI DEGLI STUDI DI CAGLIARI (IT); LAC) 29 November 2001 (2001-11-29) the whole document ----	1-57

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9401443	A	20-01-1994	AU CA CN EP WO JP MX ZA	4508593 A 2139132 A1 1087089 A 0648218 A1 9401443 A1 7508531 T 9303985 A1 9304742 A	31-01-1994 20-01-1994 25-05-1994 19-04-1995 20-01-1994 21-09-1995 28-02-1994 03-01-1995
WO 9816184	A	23-04-1998	AU AU BR CA CA CN CN CN CZ EP EP EP HU JP JP NO NO NO NZ NZ NZ PL SI SK US WO AU AU BR CN CN CN EP EP HU JP JP NO NO NO PL SI SK WO	727177 B2 4899997 A 9714349 A 2322053 A1 2323791 A1 1286258 A 1296011 A 1233254 A 9901267 A3 1072607 A2 0961775 A2 0001186 A2 2001524936 T 2002105096 A 991784 A 20004326 A 20004328 A 505531 A 505553 A 505554 A 332694 A1 20024 A 48199 A3 2002058635 A1 9816184 A2 736075 B2 6023898 A 9807473 A 1312254 A 1289594 A 1253504 T 1103559 A1 0998293 A1 0001526 A2 2002515892 T 2002080490 A 993439 A 20004327 A 20004329 A 336579 A1 9820003 A 94099 A3 9830223 A1	07-12-2000 11-05-1998 14-11-2000 16-07-1998 23-04-1998 07-03-2001 23-05-2001 27-10-1999 14-07-1999 31-01-2001 08-12-1999 28-05-2001 04-12-2001 10-04-2002 15-06-1999 15-06-1999 15-06-1999 31-08-2001 30-11-2001 30-11-2001 27-09-1999 29-02-2000 18-01-2000 16-05-2002 23-04-1998 26-07-2001 03-08-1998 21-03-2000 12-09-2001 04-04-2001 17-05-2000 30-05-2001 10-05-2000 28-05-2001 28-05-2002 19-03-2002 13-09-1999 13-09-1999 13-09-1999 03-07-2000 30-06-1999 11-06-2001 16-07-1998
WO 9405687	A	17-03-1994	AU CA EP WO JP	4973393 A 2143834 A1 0658166 A1 9405687 A1 8504753 T	29-03-1994 17-03-1994 21-06-1995 17-03-1994 21-05-1996

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 0468352	A	29-01-1992	AU	642031 B2		07-10-1993
			AU	8125391 A		30-01-1992
			CA	2047644 A1		25-01-1992
			CN	1059524 A , B		18-03-1992
			EP	0468352 A2		29-01-1992
			JP	5001044 A		08-01-1993
			US	5374625 A		20-12-1994
US 5102873	A	07-04-1992		NONE		
US 4755594	A	05-07-1988	AU	592728 B2		18-01-1990
			AU	6797287 A		06-08-1987
			CA	1270821 A1		26-06-1990
			DK	46687 A		01-08-1987
			EP	0232813 A2		19-08-1987
			FI	870371 A		01-08-1987
			KR	9100602 B1		28-01-1991
			NO	870390 A , B,		03-08-1987
			NZ	219128 A		29-01-1990
			PH	23342 A		14-07-1989
			PT	84226 A , B		01-02-1987
			JP	62228095 A		06-10-1987
			ZA	8700120 A		31-08-1988
US 5998387	A	07-12-1999	US	5736528 A		07-04-1998
			US	5631260 A		20-05-1997
			US	5446046 A		29-08-1995
			AU	728439 B2		11-01-2001
			AU	1522097 A		28-07-1997
			BR	9612324 A		28-12-1999
			CA	2238736 A1		10-07-1997
			EP	1019426 A1		19-07-2000
			JP	2000502712 T		07-03-2000
			NZ	326608 A		28-04-2000
			NZ	502628 A		29-06-2001
			WO	9724363 A1		10-07-1997
			US	5668139 A		16-09-1997
			AT	187726 T		15-01-2000
			AU	699630 B2		10-12-1998
			AU	1044995 A		22-05-1995
			CA	2172726 A1		04-05-1995
			DE	69422191 D1		20-01-2000
			DE	69422191 T2		25-05-2000
			DK	725782 T3		13-06-2000
			EP	0725782 A1		14-08-1996
			ES	2141913 T3		01-04-2000
			GR	3032730 T3		30-06-2000
			JP	9507052 T		15-07-1997
			JP	2002105094 A		10-04-2002
			PT	725782 T		31-05-2000
			WO	9511904 A1		04-05-1995
US 3891623	A	24-06-1975	DE	2122991 A1		16-11-1972
			BE	783026 A1		06-11-1972
			CH	579585 A5		15-09-1976
			CS	171723 B2		29-10-1976
			FR	2135249 A5		15-12-1972
			GB	1395764 A		29-05-1975

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/09633

Patent document cited in search report	Publication date		Patent family member(s)	Publication date	
US 3891623	A	NL	7206058 A	07-11-1972	
US 4526988	A	02-07-1985	AT 29726 T AU 565856 B2 AU 2537484 A BG 40814 A3 CA 1218647 A1 CA 1223869 C CS 246075 B2 CY 1489 A DD 216468 A5 DE 3466224 D1 DK 114484 A ,B, DK 190590 A EP 0122707 A1 ES 530364 D0 FI 840890 A ,B, GB 2136425 A ,B GB 2172287 A ,B GR 81845 A1 HK 44989 A HU 193893 B IE 57071 B1 IL 71143 A IL 80463 A JP 1986188 C JP 6009602 A JP 6102655 B JP 1833350 C JP 5042438 B JP 59175498 A KE 3874 A KR 8601283 B1 LU 88791 A9 MX 9203246 A1 NZ 207358 A PH 23240 A PH 23593 A PL 246601 A1 PT 78181 A ,B RO 89963 A1 SG 21889 G SU 1442076 A3 US 4808614 A US 5015743 A US 5118820 A US 4692434 A ZA 8401605 A	15-10-1987 01-10-1987 13-09-1984 16-02-1987 03-03-1987 07-07-1987 16-10-1986 08-12-1989 12-12-1984 22-10-1987 11-09-1984 10-08-1990 24-10-1984 01-12-1985 11-09-1984 19-09-1984 17-09-1986 12-12-1984 09-06-1989 28-12-1987 22-04-1992 31-07-1988 31-07-1988 08-11-1995 18-01-1994 14-12-1994 29-03-1994 28-06-1993 04-10-1984 30-06-1989 05-09-1986 05-11-1996 31-07-1992 06-03-1987 06-06-1989 11-09-1989 13-08-1985 01-04-1984 30-09-1986 14-07-1989 30-11-1988 28-02-1989 14-05-1991 02-06-1992 08-09-1987 30-10-1985	
WO 0190121	A	29-11-2001	AU 7490601 A WO 0190121 A2	03-12-2001 29-11-2001	